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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/010,377	01/21/1998	S.A. RUBIN	015270-00430	8602
7590 06/16/2004 Teresa Stanek Rea, ESQ Burns Doane Swecker & Mathis, LLP 1737 King Street, Suite 500 Alexandria, VA 22314			EXAMINER GAMBEL, PHILLIP	
			ART UNIT 1644	PAPER NUMBER
DATE MAILED: 06/16/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/010,377

**Applicant(s)**

RUBIN ET AL.

**Examiner**

Phillip Gambel

**Art Unit**

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2003.  
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 20-22 is/are pending in the application.  
4a) Of the above claim(s) 21 and 22 is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 1-18, 20 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_.  
5) ☐ Notice of Informal Patent Application (PTO-152)  
6) ☐ Other: \_\_\_\_\_.

### DETAILED ACTION

1. Applicant's amendment, filed 4/5/03, has been entered.

Claims 1-18 and 20-22 are pending.

Claim 19 has been canceled previously.

Claims 21-22 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 1-18 and 20 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Action will be in response to applicant's amendment, filed 4/5/03. The rejections of record can be found in the previous Office Action.

3. Claims 1-8, 11, 14-18 (and non-elected claim 21) stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification, does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 4/5/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments, filed 4/5/03 and the examiner's rebuttal are essentially the same of record.

Again, applicant asserts that the specification does teach how to find and screen various agents, including antibodies, peptides and small molecules, for the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

As applicant has acknowledged, the specification provides for methods to test for other potential therapeutic agents for the appropriate binding specificity and/or the capacity to block the interaction of VLA-4 with inflamed endothelial cells, VCAM-1 expressing cells or purified VCAM-1.

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Therefore as pointed out previously, in providing a description on how to conduct screening assays, the specification essentially calls for the use of trial and error to attempt to find a compound that has the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. There is insufficient guidance in the way of selecting a particular compound or narrowing the range of candidates in order to find a suitable compound without the need of undue experimentation, other than "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification and known in the prior art. The instant application provides for assays for identifying agents which possess certain desired characteristics and identifies certain broad categories of agents that might work amounts to a starting point or a direction for further research. The specification does not provide sufficient guidance or specificity as to execute the plan or invitation for the skilled artisan to experiment practicing the invention, encompassed by the scope of the claimed agents employed in the claimed methods.

Applicant has argued that pages 9-10 and 15 provides for agents that specifically inhibit VCAM-1 binding to the  $\alpha$ 4 subunit of VLA-4.

Again, as pointed out previously, the disclosure of particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification; such peptides are considered enabled.

It is noted that these peptides are disclosed in WO 96/01644.

Again, applicant should recite these peptides in the claims.

With respect to the claims under consideration, it has been noted that the original claims recited only with "antibodies that bind the alpha-4 subunit of VLA-4". In furthering the prosecution of the instant application with respect to the instant claims that recite "an agent that inhibits the binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin", this scope rejection has indicated enabled species disclosed in the specification as filed, rather than limiting applicant to "antibodies that bind the alpha-4 subunit of VLA-4" as the originally presented invention.

In traversing the position that the peptides disclosed in WO 96/22966; WO 96/20216; WO 96/00581 and WO 9606108 do not need to be incorporated by reference, applicant has asserted that the reliance on the disclosure of other peptides disclosed in WO 96/22966; WO 96/20216; WO 96/00581 and WO 9606108 does not constitute essential subject matter. In addition to the reliance on the identification of certain agents disclosed in the specification, applicant submits that other reagents can be identified by various routine methods and well within the purview of the skilled artisan. Such assertions are not found convincing for the reasons of record and that set forth herein.

Also, applicant's comments have included the argument that the claims are drawn to methods and not directed to specific agents, which have not been found convincing in that the claimed methods rely upon specific agents in order to treat viral encephalitis. Similarly, applicant's submission that the identify of the agents are not essential materials does not comport with the ability to make and use agents to treat viral encephalitis, as encompassed by the claimed methods.

Again, applicant appears to rely upon the disclosure of other peptides disclosed in WO 96.22966; WO 96/20216; WO 96/00581 and WO 9606108 as well as U.S. Patent No. 5,510,332 (1449; #AB).

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Here, it appears applicant is attempting to incorporate by reference essential subject matter to non-U.S. Patents.

In contrast to relying upon either SEQ ID NOS: 3/4/5 or U.S. Patent No. 5,510,332 which are disclosed in the instant specification as filed; applicant is attempting to incorporate by reference essential subject matter either to non-U.S. Patents or to material not disclosed in the application as filed.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper No. 28.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Again, applicant is invited to recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification into the claimed methods.

It is noted that recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 are recited in claim 22, which has been withdrawn from consideration. However, claim 1 is not limited to "antibodies that bind alpha 4" and SEQ ID NOS: 3/4/5.

Otherwise, applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record, as the claims read on any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

Applicant's arguments have not been found persuasive with the breadth of "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin."

5. Claims 1-2, 4-8, 11, 16, 18 and 20 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Thorsett et al. (U.S. Patent No. 6,001,809) (see entire document) in further evidence of The Merck Manual of Diagnosis and Therapeutics, 16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, NJ, 1992, pages 1472-1474) for the reasons of record.

Applicant's arguments, filed 4/5/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant acknowledges that a secondary reference has been held proper in a rejection under 35 USC 102 when it explains the meaning of a term used in the primary reference and when it shows that a characteristic not disclosed in the reference is inherent and yet does not understand why the secondary reference is appropriate.

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As pointed out previously, the Merck Manual teach viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex (see pages 1472-1474). In addition, meningitis with no evidence of bacterial organisms is considered aseptic and caused by viral infections (see pages 1472-1474). Therefore, one of ordinary skill in the art would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis at the time the invention was made.

Therefore, the secondary reference when it explains the meaning of a term used in the primary reference and when it shows that a characteristic not disclosed in the reference is inherent.

Applicant asserts that the reference does not teach that the patient is free of multiple sclerosis. However, applicant has not shown why the ordinary artisan would assume that the prior art taught that the patient with viral encephalitis was a patient with multiple sclerosis.

The following of record is reiterated herein for applicant's convenience.

Thorsett et al. teach methods of treating viral encephalitis (e.g., see column 10, paragraph 2) with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4-mediated adhesion, wherein the oligopeptides are selected via sequence analysis with antibodies that inhibit VLA-4 binding to VCAM-1 (see entire document, including Description of the Preferred Embodiments, including column 5). The pharmaceutical compositions can be administered as prophylaxis or therapy in a patient already suffering from the disease or at least partially arrest the symptoms of the diseases or complications (column 10, paragraph 5). Amounts effective for use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient (column 10, paragraph 5). Therefore, the prophylactic and therapeutic administration comprises monitoring the patient.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit or block cellular adhesion associated a number of disorders and diseases including viral meningitis and encephalitis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

The Merck Manual teach viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex (see pages 1472-1474). In addition, meningitis with no evidence of bacterial organisms is considered aseptic and caused by viral infections (see pages 1472-1474). Therefore, one of ordinary skill in the art would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis at the time the invention was made.

It is acknowledged that the elected invention is drawn to using anti-VLA-4 / anti alpha-4 antibodies in the claimed methods. However, given the application of Thorsett et al. (U.S. Patent No. 6,001,809) in the obviousness rejection under 35 USC 103 below, Thorsett et al. is applied here in a rejection under 35 USC 102(e) since it anticipates the broad claims encompassing "agents".

Applicant's arguments have not been found persuasive.

6. Claims 1-18 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thorsett et al. (U.S. Patent No. 6,001,809) in view of The Merck Manual of Diagnosis and Therapeutics, 16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, NJ, 1992, pages 1472-1474) and Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Yednock et al. (U.S. Patent No. 6,033,665) for the reasons of record.

Applicant's arguments, filed 4/5/03, have been fully considered but are not found convincing essentially for the reasons of record.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

Although applicant asserts that the ordinary artisan in the art would not believe that the treatment of one condition would correspondingly treat the other.

However, the prior art references do provide for treating encephalitis, including viral encephalitis, with inhibitors of VLA-4. Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Bendig et al. AND/OR Yednock to those of Thorsett et al. to substitute inhibitory VLA-4 $\alpha$ -specific antibodies in the treatment of viral encephalitis, given the same properties of the referenced VLA-4 $\alpha$ -specific antibodies and VLA-4 $\alpha$ -specific peptides and the same therapeutic endpoints of inhibiting inflammatory responses, including in the brain

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Bendig et al. AND/OR Yednock to those of Thorsett et al. to substitute inhibitory VLA-4 $\alpha$ -specific antibodies in the treatment of viral encephalitis, given the same properties of the referenced VLA-4 $\alpha$ -specific antibodies and VLA-4 $\alpha$ -specific peptides and the same therapeutic endpoints of inhibiting inflammatory responses, including in the brain.

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In contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard; it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967). The evidence of purported unobvious results of record in this application is insufficient to overcome the inference of fact in this case.

Therefore the above claims remain rejected under 35 USC 103 for the reasons of record and reiterated herein for applicant's convenience.

With respect to the assertion of unexpected results, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Thorsett et al. teach methods of treating viral encephalitis (e.g., see column 10, paragraph 2) with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4-mediated adhesion, wherein the oligopeptides are selected via sequence analysis with antibodies that inhibit VLA-4 binding to VCAM-1 (see entire document, including Description of the Preferred Embodiments, including column 5).

Thorsett et al. also teach that the pharmaceutical compositions can be administered as prophylaxis or therapy in a patient already suffering from the disease or at least partially arrest the symptoms of the diseases or complications (column 10, paragraph 5).

Amounts effective for use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient (column 10, paragraph 5). Although the primary reference differs from the claimed methods of monitoring the patients for encephalitis per se, the prior art teachings of prophylactic and therapeutic administration comprises monitoring the patient or would make obvious to monitor the condition of the treated patient to one of ordinary skill in the art at the time the invention was made. In addition, The Merck Manual teach Diagnosis of patients with viral encephalitis and aseptic meningitis (pages 1472-1475). Here, asymptomatic symptoms and signs known to one of ordinary skill at the time the invention was made are indicated (page 1473).



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In addition, the Merck Manual teach the Etiology, Pathology, Diagnosis and Prognosis and Treatment of viral encephalitis and aseptic meningitis. The Merck Manual teach viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex (see pages 1472-1474). In addition, meningitis with no evidence of bacterial organisms is considered aseptic and caused by viral infections (see pages 1472-1474). Therefore, one of ordinary skill in the art would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis at the time the invention was made.

Although Thorsett et al. teach the use of anti-VLA-4 / anti- $\alpha 4$  antibodies in screening for inhibitory VLA-4-specific oligopeptides, Thorsett et al. differs from the claimed methods by explicitly teaching that anti-VLA-4 / anti- $\alpha 4$  as the inhibitory VLA-4-specific agent.

Bendig et al. teach using inhibitory VLA-4 $\alpha$ -specific antibodies, including humanized antibodies and the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16). Therefore, the anti-VLA-4 / anti- $\alpha 4$  antibody specificities as well as antibody forms and compositions encompassed by the claims (e.g. claims, 8-13 and 20).

Yednock teaches the using inhibitory VLA-4 $\alpha$ -specific antibodies, including humanized antibodies and the 21.6 specificity to treat brain inflammation, including meningitis (see entire document, including Detailed Description of the Invention and Claims). Therefore, the anti-VLA-4 / anti- $\alpha 4$  antibody specificities as well as antibody forms and compositions encompassed by the claims (e.g. claims, 8-13 and 20).

Although the primary reference differs from the claimed methods pediatric nature of the patients or providing antiviral/anti-inflammatory agents in addition per se, it would have been obvious to one of ordinary skill at the time to provide all patients in need, including pediatric patients with inhibitory VLA-4 $\alpha$ -specific antibodies to inhibit viral encephalitis and to provide said VLA-4 $\alpha$ -specific antibodies in combination with other current or standard therapeutic regimens such as antiviral or anti-inflammatory agents in order to target the virus or its effects in order to treat viral encephalitis.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Bendig et al. AND/OR Yednock to those of Thorsett et al. to substitute inhibitory VLA-4 $\alpha$ -specific antibodies in the treatment of viral encephalitis, given the same properties of the referenced VLA-4 $\alpha$ -specific antibodies and VLA-4 $\alpha$ -specific peptides and the same therapeutic endpoints of inhibiting inflammatory responses, including in the brain. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. No claim is allowed.

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8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Phillip Gambel, PhD.  
Primary Examiner  
Technology Center 1600  
June 14, 2004